REMARKS

This document is filed in reply to the final Office Action dated September 22, 2004 ("Office Action") in view of the previous final office action dated December 17, 2003 ("Previous Office Action"). Claims 24-33, 35-39, and 41-49 are pending. Reconsideration of this application is requested in view of the following remarks:

All pending claims remain rejected for obviousness over U.S. Patent 5,958,891 to Hsu et. al. ("Hsu") and Janeway Jr. et. al. Immunobiology, 1999 ("Janeway") in view of Pouwels et. al. Intl. J. Food Micorbiol. 1998 ("Pouwels") and Medaglini et. al. PNAS, 1995 ("Medaglini"). See the Office Action, the paragraph bridging pages 2 and 3.

Applicants respectfully traverse and will discuss independent claim 24 first. Claim 24 is drawn to a method of decreasing the production of IgE in a subject exposed to a dust mite allergen. The method requires, among others, orally administering to a subject a non-pathogenic, Gram-positive bacterium that contains a nucleotide sequence encoding a dust mite allergen (a prokaryotic expression system). In other words, the method requires using a prokaryotic expression system to deliver an allergen to a subject. According to the Examiner,

> Hsu et. al. teaches a method of suppressing allergen-specific IgE production in a subject [via an eukaryotic expression system] comprising administering to [a] subject a recombinant plasmid ...encoding an allergen ... [by] intramuscular, intranasal, and intratracheal routes, ... Hsu et. al. do not teach using a Gram-positive bacterium [, a prokaryotic expression system,] as the expression vehicle.
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> Janeway Jr. teaches in the context of treating allergy (desensitization) and inhibiting IgE production, "In desensitization, the aim is to shift the antibody response away from an IgE-dominated response ... towards one dominated by IgG. ... Janeway Jr. does not discuss the detail with respect to how the antigenic peptide is being delivered.
>
> Pouwels et. al. teach that lactic acid bacteria is a family of non-pathogenic, Gram-positive bacterium that could be genetically modified for use as antigen delivery vehicles for oral immunization purpose. ... Pouwels et. al. do not particularly teach using the [lactic acid bacteria] system for expressing allergens for desensitization.
>
> Medaglini et. al. teach another non-pathogenic, Gram-positive bacterium system *Streptococuus gordonii*, which [is orally administered to mice to generate] significant IgG immune response to [a] specific allergen. ... Medaglini et. al. do not measure IgE nor express a dust mite allergen.

See the Previous Office Action, page 5, line 3 through page 7, line 3. The Examiner asserted that Janeway would have motivated one skilled in the art to suppress IgE production by increasing

IgG level, e.g., by administering an allergen via the prokaryotic expression system of Pouwels or Medaglini. In view of Hsu's success in using a eukaryotic expression system, the Examiner further asserted that there would be an expectation of success in using a prokaryotic expression system as well. This assertion is based on the assumption that "the plasmid [in the eukaryotic expression system taught in Hsu] and the recombinant Gram-positive bacterium [in the prokaryotic expression system taught in Pouwels or Medaglini] are functionally equivalent in presenting antigen to the immune system of a eukaryotic animal [, and] the difference in [the two systems] has not effected the efficiency of antigen-presentation, nor the induction nor the nature of an expected immune response to an antigen." See, the Previous Office Action, page 8, line 16 through page 9, line 5. The Examiner then proceeded to conclude that it would have been prima facie obvious to one skilled in the art to modify Hsu's IgE production-suppressing method by replacing the eukaryotic expression system with the prokaryotic expression system taught in Pouwels or Medaglini.

Applicants disagree. In the Declaration filed with the response dated September 9, 2003, Applicants already pointed out a key difference between a eukaryotic expression system and a prokaryotic expression system. More specifically, an antigen delivered by a eukaryotic expression system is presented to $CD8^+$ T cells. In contrast, an antigen delivered by an prokaryotic expression system is presented to $CD4^+$ T cell. It is well known that $CD8^+$ T cells and $CD4^+$ T cells play different roles in IgE production. In fact, according to Hsu,

> An important component of [down-regulation of immune responses] is the selective suppression of Th2-dependent IgE response to inhaled or fed Ags, which is mediated by Ag-specific $CD8^+$ T cells ... **$CD8^+$ T cells** may regulate IgE production by **suppressing IgE synthesis** via the inhibitory effect of IFN-r on B cells and/or by affecting the differentiation and function of Th2-like **$CD4^+$ T cells, which support IgE production**. (Emphasis added)

See, column 2, lines 19-29. Put differently, Hsu specifically teaches that (1) $CD8^+$ T cells suppress IgE synthesis, and (2) $CD4^+$ T cells support IgE production. Thus, contrary to the Examiner's assumption, the eukaryotic expression system taught in Hsu and prokaryotic expression system taught in Pouwels/Medaglini, are not functionally equivalent in presenting antigen to the immune system of a eukaryotic animal. Moreover, to the extent that Hsu explicitly teaches that "$CD4^+$ T cells ... support IgE production," it teaches away from using a prokaryotic expression system, which presents an antigen to $CD4^+$ T cells, for suppressing IgE production.

In view of this teaching, one skilled in the art would have no motivation or expectation of success to use a prokaryotic expression system in suppressing IgE production, as required in claim 24. Thus, the Examiner failed to establish a prima facie case of obviousness.

Even if a prima facie case of obviousness were made, which Applicants do not agree, it can be successfully rebutted by a showing of an unexpected advantage of the method of claim 24. According to the Examiner, "enhancing an IgG production is ... a regulatory mechanism for [suppressing IgE production and] treating allergy." See the Previous Office Action, page 10, lines 1 and 2; and the Office Action, page 4, lines 8-10. It is her position that an IgE production suppressing method suggested by the four cited reference would lead to an increased level of allergen-specific IgG; in other words, it would be expected that suppressed IgE production is associated with increased IgG production. As described in the working example of the Specification, mice treated by the claimed method showed "more than 80% inhibition" of allergen-specific IgE production. However, unexpectedly, the claimed method did not cause any significant change in allergen-specific IgG production. See, e.g., page 9, lines 6-21.

In this connection, Applicants note that, according to Janeway, increased production of allergen-specific IgG also leads to hypersensitivity and tissue damage, and therefore is undesired. See, e.g., Fig, 12-2. Thus, the method of claim 24 clearly posses at least one unexpected advantage, i.e., suppressing allergen-specific IgE production without causing an increase of undesired allergen-specific IgG. On this additional ground, claim 24 is clearly not rendered obvious by the four cited references.

Independent claims 36, 43, and 44 are drawn to methods of decreasing production of IgE or relieving bronchopulmonary congestion caused by increased production of IgE. All of the methods require orally administering to a subject a non-pathogenic, Gram-positive bacterium for expressing an allergen (i.e., a prokaryotic expression system). For the same reasons set for above, they are not rendered obvious by the four cited references. Neither are claims 25-33, 35, 37-39, 41, 42, and 45-49, all of which depend from claim 24, 36, 43, or 44.

CONCLUSION

Applicants submit that the grounds for the rejection asserted by the Examiner have been overcome, and that claims, as pending, define subject matter that is non-obvious. Thus, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Please apply any charges to deposit account 06-1050, referencing attorney docket 12774-002001.

Respectfully submitted,

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